REMARKS

In the claims

Claims 1–32 are canceled without prejudice or disclaimer. Claims 33–54 are added by this paper.

Claim Amendments

New claims 33–54 are inventive over the cited references and are supported by the disclosure contained in the entire specification, as originally filed.

Specification

The specification has been amended as per the Examiner's suggestion. Withdrawal of the objection is courteously requested.

Rejections under 35 U.S.C. § 101 and § 112, second paragraph

The rejections not specifically discussed herein are moot in view of the amendments. Withdrawal of the rejection is courteously requested.

Rejection under 35 U.S.C. § 112, first paragraph (Writtten Description)

At page 6, the Office Action alleges claims 12–15 and 23 and 29 fail to provide an adequate written description of the invention and fail to comply with the enablement requirement. More specifically, page 7 of the Office Action alleges that the "specification does not provide evidence that the claimed biological materials are (1) known [*i.e.*, publicly available] (2) reproducible [*i.e.*, sequenced] or 3) deposited." Applicants respectfully disagree with this contention.

It is respectfully submitted that the specification provides adequate guidance regarding the antibody species claimed herein. More specifically, the specification discloses the antibody species recited in Applicants' claim 33 is the subject of numerous

patent publications. It is taught that monoclonal antibody 425 (MAb425), which is the subject of US 5,558,864 and EP 0531 472 and chimeric monoclonal antibody 225 (c MAb 225), which is the subject of US 4,943,533 and EP 0359 282, are both directed to the EGF receptor. See, for example, page 4, lines 11–22 of the instant specification.

The Office is requested to review the cited reference of Bendig et al. ('864 patent) and Mendelsohn et al. ('533 patent). For example, Bendig teaches a monoclonal antibody directed against EGFR and recites the structural elements comprising constant, hypervariable, and framework regions of such antibody molecules. Similarly, Mendelsohn discloses c 225 monoclonal antibody-secreting hybridoma cells and chimeric antibodies (c MAb 225) derived from such cells. The cited references further disclose that the claimed antibody molecules and/or their respective hybridomas are on deposit with American Type Culture Collection (ATCC) with the catalog Nos. HB 9629 (for MAb425) and CRL HB8507 (for c MAb 225). As such, it is courteously submitted that the structure/function aspects of the antibody species recited herein were fully disclosed by the combined disclosure of Applicants' instant specification and the references cited therein.

It is further submitted that the discipline, on which Applicants' instant invention is based, was mature prior to the filing of the instant application. For instance, a PUBMED search of "MAb 425 antibody" revealed more than 60 scientific publications before the earliest priority date of the instant application. A parallel search with "MAb 225 antibody" revealed more than 100 such publications. The specification need not disclose, and preferably omits, what is well known to those skilled in the art. See, e.g., *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). See, also, MPEP §2164.05(a). Indeed, the Federal Circuit found that an application, which failed to disclose the amino acid sequence of a claimed protein, was not deficient in the written description requirement, despite the fact that the undisclosed sequence was an essential part of the protein's description. See, *Capon v. Eshhar v. Dudas*, (Fed. Cir. 2005) 418 F.3d 1349, 76 U.S.P.Q.2d 1078. Likewise, in the instant application, the specification need not provide expressed guidance on the structural features of the claimed antibodies, as such were not only known, but also commercially available to a skilled worker before the application was filed.

In light of these arguments and remarks, it is respectfully submitted that Applicants' disclosure more than reasonably conveys to one of ordinary skill in the art that, as of the filing date, Applicants' had possession of the claimed subject matter. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

Pages 8–16 of the Office Action alleges that the "specification does not directly describe epitopes located within the receptor-binding domain of EGFR, its ligands, or antibodies/antibody variants directed against such receptors." See page 14, 2nd paragraph. As such, claims 1, 2, 4–8, 10, 12–15, and 18–32 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

In view of the mature state of the art at the time of the filing, a skilled worker could, using routine techniques, reliably and accurately screen for the species of antibodies that are commensurate with the claimed invention. Applicants respectfully submit that the instant specification, coupled with a skilled worker's knowledge, provides adequate written description guidance as to the structural and functional aspects of the compounds claimed herein. Guidance for the structural aspect of the claimed compounds is, for example, provided by the individual amino acid sequences of the receptor and conventional antibodies, which were readily available to a skilled worker before the filing date of the instant application. Guidance for the functional aspect of the claimed antibodies is, for example, provided by the disclosure of the antibodies having the capability to bind to EGF receptor (EGFR). Additionally, the reagents or tools for successful antibody design, comprising, for example, manipulating the amino acid composition and/or length of the constant (F_c) region or variable $F(ab)_2$ regions, were commonly available to an average skilled worker. The activity of the claimed antibodies or fragments thereof could be routinely screened using applicable *in vitro* or *in vivo* techniques, since the biology of EGFR, both at the molecular as well as physiological level, was well-established before the filing date of the instant application.

Given this maturity in the field, a skilled worker could routinely screen for any variant

or fragment of the claimed antibodies in order to practice the instant invention in its broadest possible scope. Nothing more than routine experimentation would be required. It is therefore courteously submitted that Applicants' claims in the current form, with adequate support from the specification, fully comply with the statutory requirements under 35 U.S.C. § 112, first paragraph, as specified in the PTO's own guidelines. (See below regarding single-point mutations). Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

The specification coupled with a skilled worker's knowledge provides adequate guidance to make and use the claimed compounds. The specification provides both general and specific guidance regarding the biological activity and utility of the bispecific antibodies and fragments thereof. See, for example, Examples 1–3 and the disclosure contained in pages 1–4 of the instant specification. In the absence of evidence which demonstrate otherwise, all claims must be taken to satisfy the requirements of 35 U.S.C. § 112, first paragraph. Moreover, only one use needs to be enabled for compound claims. Here, we focus on the monoclonal antibodies h MAb 425 and c MAb 225.

The specification provides guidance on the synthetic design and use of the claimed antibodies. In light of the disclosure, the courts have placed the burden on the PTO to show otherwise. It is courteously submitted that the Examiner has not presented any evidence to refute the findings or the conclusions made in these supporting publications. In addition, no evidence has been presented to support the contention that the claimed antibodies, variants and/or fragments thereof could not be made and used, in a manner that is commensurate with Applicants' claimed invention. Only unsupported allegations and conclusions regarding the "complexity" and "unpredictability" of the "broad genus of compounds" are provided to support the contention. There are especially weak in the face of the showing that the field of EGFR epitopes and antibodies is a mature one.

In view of the above remarks, it is respectfully submitted that applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is routine with in the art. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully

requested.

Rejection under 35 U.S.C. § 103(a)

The rejection of the claims under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fan et al. in view of Robert et al. and Zhu et al is respectfully traversed.

The Office Action at pages 17–21 alleges that it would have been *prima facie* obvious to one of ordinary skill in the art to design the claimed bispecific antibody comprising two anti-EGFR monoclonal antibody fragments and immunoconjugates thereof using the cited disclosure of Fan Robert, and Zhu. Applicants courteously disagree with this contention and maintain that the Office Action fails to meet the basic criteria for establishing *prima facie* case of obviousness. In this regard, the MPEP expressly states:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to *make the claimed combination* and the reasonable expectation of success *must both be found in the prior art, and not based on applicant's disclosure*. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143.

Fan et al.'s disclosure is drawn to the anti-EGFR monoclonal antibodies mAb225 and mAb528, $F(ab')_2$ fragments and uses thereof, particularly against EGFR signaling mediated by EGF and TGF-α. See, col. 2, lines 9–18 at page 4322 of Fan et al. As recited at page 19 of the Office Action, "Fan does not teach a bispecific antibody having the capability to bind to *different* epitopes located on the same EGF receptor molecule type." It therefore goes without saying that Fan's anti-EGFR antibodies do not encompass the structural aspects of the antibodies claimed herein.

The Office Action then alleges that the deficiencies of Fan are compensated by Robert's and Zhu's disclosure of bispecific antibodies. However, it is respectfully submitted that Roberts' bispecific antibodies are drawn against carcinoembryonic antigen (CEA), a

protein that is unrelated to the subject matter of the instant invention. See, col. 2, lines 1–21 at page 285 of Robert et al for a brief disclosure on CEA proteins. Similarly, Zhu's bispecific antibodies are directed against human kinase insert domain-containing receptors (KDR). See, section [0017] at page 2 of the specification and FIG. 3 of Zhu et al. Zhu also teaches that in another embodiment, the bispecific antibodies are directed against FMS-like tyrosine kinase (Flt-1) receptors.

In the last paragraph at page 19 of the Office Action, it is alleged that Zhu teaches a monoclonal antibody (C225) or an IgG1 antibody against EGFR in a manner taught by the instant invention. Applicants respectfully submit that this contention is grossly misplaced. Zhu merely uses the EGFR antibodies as controls. For example, in FIG. 4B, Zhu discloses that C225, a chimeric antibody directed against human EGFR, does not bind to either KDR or FLK-1 antigens. In FIG. 5, it is taught that C225 showed no effect on KDR binding to VEGF. See, sections [0151] and [0154] of the cited reference. In either case, Zhu did not use a bispecific antibody having the capability to bind to *different* epitopes located on the same EGF receptor molecule type. On the contrary, Applicants find that Zhu's teaching teaches away from what is claimed by the instant invention. For example, section [0062] at page 7, Zhu expressly states:

> Certain bispecific antigen-binding proteins of the invention bind to two of the above listed receptors. In one preferred embodiment, such a bispecific antigen-binding protein binds to HER2 and EGF-R. In a second preferred embodiment, an antigen-binding protein of the invention binds to KDR and FLT-1. (Emphasis added)

Applicants respectfully submit that a combination of Fan, Robert, and Zhu, even at its broadest scope, fails to encompass the structural limitations of the compounds claimed herein. As such, a combination of the cited references would never lead to the reformulation of the prior art to arrive at what is claimed by the instant invention. Furthermore, since none of the cited references impart any teaching or suggestion regarding the claimed compounds, one of ordinary skill in the art would not have been motivated to combine the cited references. Even if one were to combine this teaching of all references, there would be no way, absent hindsight, to arrive at the claimed structures.

The Office Action is merely alleging one could arrive at this from the prior art. But this is insufficient. It is required that the PTO establish that one of ordinary skill would

arrive at the claimed invention from the references. Therefore, it is respectfully submitted that the Office Action has failed to meet the basic criteria for *prima facie* case of obviousness, and as such, the rejection under 35 U.S.C. §103(b) must be withdrawn.

Claims drawn to pharmaceutical compositions

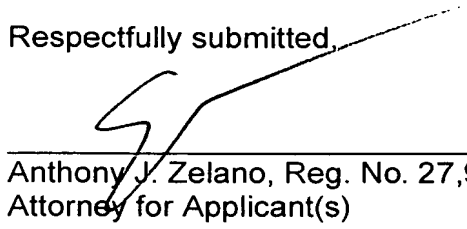
The Office Action at page 21 alleges that the claims drawn to a pharmaceutical composition are rendered obvious when the aforementioned references are taken together with the teachings of Albanell et al. and/or Kim et al.

The various deficiencies of Fan, Robert and Zhu have been previously outlined. The Examiner is courteously requested to take note of these deficiencies. The additionally cited references of Albanell et al. and Kim et al. are generically drawn to monoclonal antibodies directed against HER-2. See, page 22 of the open Office Action. It is courteously submitted that the rejection is moot in view of the claim amendments. For example, see new claim 33, and the claims dependent therefrom. Withdrawal of the rejection is courteously requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

Enclosed is a check in the amount of $120.00 for the one-month extension-of-time fees. No other fees are believed to be due with this response; however, the Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,



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